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## (54) Combinations of Formoterol and Mometasone Furoate for Asthma

(57) A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or a solvate of the salt and (B) mometasone furoate, for simultaneous, sequen-

tial or separate administration in the treatment of an inflammatory or obstructive airways disease.

## Description

[0001] This invention relates to combinations of a beta-2 agonist and a steroid and their use for the treatment of inflammatory or obstructive airways diseases.

5 [0002] Formoterol, N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)-ethyl)phenyl]formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases. Mometasone furoate, (11 $\beta$ , 16 $\alpha$ )-9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-pregna-1, 4-diene-3,20-dione, alternatively designated 9 $\alpha$ ,21-dichloro-16 $\alpha$ -methyl-1,4-pregnadiene-11 $\beta$ ,17 $\alpha$ -diol-3,20-dione 17-(2'-furoate), is a topical anti-inflammatory corticosteroid which is described in US4472393.

10 [0003] It has now surprisingly been found that a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained by combination therapy using formoterol, in free form or in the form of a salt or solvate thereof, and mometasone furoate. For instance, it is possible using this combination therapy to reduce the dosages of mometasone furoate or formoterol required for a given therapeutic effect considerably compared with those required using treatment with mometasone furoate or formoterol alone, thereby minimising possibly undesirable side effects. In particular, it has been found that these combinations, particularly as compositions containing formoterol and mometasone furoate, induce an anti-inflammatory activity which is significantly greater than that induced by formoterol or mometasone furoate alone and that the amount of mometasone furoate needed for a given anti-inflammatory effect may be significantly reduced when used in admixture with formoterol, thereby reducing the risk of undesirable side effects from the repeated exposure to the steroid involved in the treatment of inflammatory or obstructive airways diseases.

15 [0004] Furthermore, using the combination therapy of the invention, particularly using compositions containing formoterol and mometasone furoate, medicaments which have a rapid onset of action and a long duration of action may be prepared. Moreover, using such combination therapy, medicaments which result in a significant improvement in lung function may be prepared. In another aspect, using the combination therapy of the invention, medicaments which provide improved control of obstructive or inflammatory airways diseases, or a reduction in exacerbations of such diseases, may be prepared. In a further aspect, using compositions of the invention, medicaments which can be used on demand in rescue treatment of obstructive or inflammatory airways diseases, or which reduce or eliminate the need for treatment with short-acting rescue medicaments such as salbutamol or terbutaline, may be prepared; thus medicaments based on compositions of the invention facilitate the treatment of an obstructive or inflammatory airways disease with a single medicament.

20 [0005] In one aspect, the present invention provides a medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or a solvate of said salt and (B) mometasone furoate, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

25 [0006] In another aspect, the present invention provides a method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined.

30 [0007] In a further aspect, the present invention provides a pharmaceutical composition comprising a mixture of effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined, optionally together with a pharmaceutically acceptable carrier.

35 [0008] The present invention also provides (A) and (B) as hereinbefore defined for use in combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

40 [0009] The invention further provides the use of (A) as hereinbefore defined or (B) as hereinbefore defined in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

45 [0010] In a yet further aspect, the present invention provides a pharmaceutical composition for use in the treatment of an inflammatory or obstructive airways disease comprising (A) and (B) as hereinbefore defined.

50 [0011] The present invention still further provides the use of (A) and (B) as hereinbefore defined for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

55 [0012] Pharmaceutically acceptable salts of formoterol include, for example, salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballylic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acids.

60 [0013] Component (A) may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, a mixture of enantiomers, a racemate or a mixture thereof. It may be in the form of a solvate, for example a hydrate, thereof, for example as described in US3994974 or US5684199, and may be present in a particular crystalline form, for example as described in WO95/05805. Preferably, component (A) is formoterol fumarate, especially in the form of

the dihydrate.

[0014] Administration of the medicament or pharmaceutical composition as hereinbefore described, i.e. with (A) and (B) in admixture or separate, is preferably by inhalation, i.e. (A) and (B) or the mixture thereof are in inhalable form.

The inhalable form of the medicament i.e. of (A) and/or (B) may be, for example, an atomizable composition such as an aerosol comprising the active ingredient, i.e. (A) and (B) separately or in admixture, in solution or dispersion in a propellant, or a nebulizable composition comprising a dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium. For example, the inhalable form of the medicament may be an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant. In another example,

5 the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium, or a combination of a dispersion of (A) in such a medium with a dispersion of (B) in such a medium.

[0015] An aerosol composition suitable for use as the inhalable form of the medicament may comprise the active ingredient in solution or dispersion in a propellant, which may be chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more

10 such hydrocarbons, and halogen-substituted hydrocarbons, for example fluorine-substituted methanes, ethanes, propanes, butanes, cyclopropanes or cyclobutanes, particularly 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3-heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where the active ingredient is present in suspension in the propellant, i.e. where it is present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those

15 lubricants and surfactants known in the art. Other suitable aerosol compositions include surfactant-free or substantially surfactant-free aerosol compositions. The aerosol composition may contain up to about 5% by weight, for example 0.002 to 5%, 0.01 to 3%, 0.015 to 2%, 0.1 to 2%, 0.5 to 2% or 0.5 to 1%, by weight of the active ingredient, based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by weight of the aerosol composition. The aerosol composition may also contain a co-solvent such as

20 ethanol in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device.

25 [0016] In another embodiment of the invention, the inhalable form is a dry powder, i.e. (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with a finely divided pharmaceutically acceptable carrier, which is preferably present and may be one or more materials known as pharmaceutically acceptable carriers, preferably chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. An especially preferred carrier is lactose. The dry powder may be in capsules of gelatin or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of (A) and/or (B) together with the carrier in amounts to bring the total weight of powder per capsule to from 5 mg to 50 mg. Alternatively, the dry powder may be contained as a reservoir in a multi-dose dry powder inhalation device.

30 [0017] In the finely divided particulate form of the medicament, and in the aerosol composition where the active ingredient is present in particulate form, the active ingredient may have an average particle diameter of up to about 10 µm, for example 0.1 to 5 µm, preferably 1 to 5 µm. The solid carrier, where present, generally has a maximum particle diameter up to 300 µm, preferably up to 212 µm, and conveniently has a mean particle diameter of 40 to 100 µm, e.g. 50 to 75 µm. The particle size of the active ingredient, and that of a solid carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray-drying, lyophilisation or recrystallisation from supercritical media.

35 [0018] The inhalable medicament may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described in association with one or more inhalation devices. In a further aspect, the invention provides an inhalation device, or a pack of two or more inhalation devices, containing a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described.

40 [0019] Where the inhalable form of the active ingredient is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100 µl, e.g. 25 to 50 µl, of the composition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992.

45 [0019] Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, for example an electronically controlled device such as an AERx (ex Aradigm,

US) or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100  $\mu$ l, than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dry powder comprising a dosage unit of (A) and/or (B) or a multidose dry powder inhalation (MDPI) device adapted to deliver, for example, 3-25 mg of dry powder comprising a dosage unit of (A) and/or (B) per actuation. Suitable such dry powder inhalation devices are well known. For example, a suitable device for delivery of dry powder in encapsulated form is that described in US3991761, while a suitable MDPI device is that described in WO97/20589.

[0020] The medicament of the invention is preferably a pharmaceutical composition comprising a mixture of (A) as hereinbefore defined and (B) as hereinbefore defined, preferably together with a pharmaceutically acceptable carrier as hereinbefore described.

[0021] The weight ratio of formoterol, or salt or solvate thereof, to mometasone furoate may be, in general, from 2:1 to 1:2000, for example from 1:1 to 1:1000, from 1:2 to 1:100, or from 1:5 to 1:50. More usually, this ratio is from 1:10 to 1:25, for example from 1:15 to 1:25. The two drugs may be administered separately in the same ratio. Specific examples of this ratio, to the nearest whole number, include 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19, 1:20, 1:21, 1:22, 1:23, 1:24 and 1:25. The above weight ratios apply particularly where (A) is formoterol fumarate dihydrate. Thus, since the molecular weights of formoterol fumarate dihydrate and mometasone furoate are 840.9 and 521.4 respectively, the corresponding molar ratios of (A) to (B) may be, in general, from 1.24:1 to 1:3227, for example from 0.62:1 to 1:1613, from 1:3.2 to 1:161, or from 1:8.1 to 1:80.7; more usually from 1:16.1 to 1:40.3, for example from 1:24.2 to 1:40.3; specific examples of the molar ratio being 1:16.1, 1:17.8, 1:19.4, 1:21, 1:22.6, 1:24.2, 1:25.8, 1:27.4, 1:29, 1:30.7, 1:32.3, 1:33.9, 1:35.5, 1:37.1, 1:38.7 and 1:40.3.

[0022] A suitable daily dose of formoterol, or salt or solvate thereof, particularly as formoterol fumarate dihydrate, for inhalation may be from 1 to 72  $\mu$ g; for example from 1 to 60  $\mu$ g, generally from 3 to 50  $\mu$ g, preferably from 6 to 48  $\mu$ g, for instance from 6 to 24  $\mu$ g. A suitable daily dose of mometasone furoate for inhalation may be from 50 to 2000  $\mu$ g, for example from 100 to 2000  $\mu$ g, from 100 to 1600  $\mu$ g, from 100 to 1000  $\mu$ g, or from 100 to 800  $\mu$ g, preferably from 200 to 500  $\mu$ g, for instance from 200 to 400  $\mu$ g. The precise dose used will of course depend on the condition to be treated, the patient and the efficiency of the inhalation device.

[0023] A suitable unit dose of formoterol component (A), particularly as formoterol fumarate dihydrate, may be from 1 to 72  $\mu$ g, for example from 1 to 60  $\mu$ g, generally from 3 to 48  $\mu$ g, preferably from 6 to 36  $\mu$ g, especially from 12 to 24  $\mu$ g. A suitable unit dose of mometasone furoate (B) may be from 25  $\mu$ g to 2000  $\mu$ g, for example from 50  $\mu$ g to 1000  $\mu$ g, preferably from 500  $\mu$ g to 800  $\mu$ g, more preferably from 100  $\mu$ g to 500  $\mu$ g, especially from 100 to 400  $\mu$ g, e.g. from 200 to 400  $\mu$ g. These unit doses may suitably be administered once or twice daily in accordance with the suitable daily dose mentioned hereinbefore. For on demand usage, a dosage unit containing 6  $\mu$ g or 12  $\mu$ g of (A) and 50  $\mu$ g or 100  $\mu$ g of mometasone furoate (B) is preferred.

[0024] In one preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder in a capsule containing a unit dose of (A) and (B), for example for inhalation from a single capsule inhaler, the capsule suitably containing, where (A) is formoterol fumarate dihydrate, from 3  $\mu$ g to 36  $\mu$ g of (A), preferably from 6  $\mu$ g to 24  $\mu$ g of (A), especially from 12  $\mu$ g to 24  $\mu$ g of (A), and from 25  $\mu$ g to 800  $\mu$ g, e.g. 25  $\mu$ g to 500  $\mu$ g or 25  $\mu$ g to 400  $\mu$ g, of (B), preferably from 50  $\mu$ g to 400  $\mu$ g of (B), especially from 100 to 400  $\mu$ g of (B), together with a pharmaceutically acceptable carrier as hereinbefore described in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50 mg, for example 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg or 50mg, preferably 20 to 25 mg, especially 25 mg.

[0025] In another preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver 3mg to 25mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is formoterol fumarate dihydrate, a powder comprising, by weight, 3 to 36 parts, preferably 6 to 24 parts, especially 12 to 24 parts of (A); 25 to 800 parts, e.g. 25 to 500 parts, preferably 50 to 400 parts, especially 100 to 400 parts of (B); and 2164 to 24972 parts, preferably 4164 to 14972 parts, especially 4164 to 9972 parts of a pharmaceutically acceptable carrier as hereinbefore described.

[0026] In accordance with the above, the invention also provides a pharmaceutical kit comprising (A) and (B) as hereinbefore defined in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts. Such a kit suitably further comprises one or more inhalation devices for administration of (A) and (B). For example, the kit may comprise one or more dry powder inhalation devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder comprising a dosage unit of (A) and capsules containing a dry powder comprising a dosage unit of (B). In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) and a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (B). In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising (A) in a propellant and a metered dose inhaler containing

an aerosol comprising (B) in a propellant.

[0027] Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

[0028] Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

[0029] Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis and emphysema, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalcosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[0030] The invention is illustrated by the following Examples, in which parts are by weight unless stated otherwise.

Example 1 - Aerosol Composition for Metered Dose Inhaler

[0031]

Ingredient	% by weight
Formoterol fumarate dihydrate	0.012
Mometasone furoate	0.250
Ethanol (absolute)	2.500
HFA 227	60.768
HFA134a	36.470

Example 2 - Dry Powder

[0032]

Ingredient	% by weight
Formoterol fumarate dihydrate	0.048
Mometasone furoate	1.000
Lactose monohydrate	98.952

Example 3

[0033] A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing 12 parts of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1.5µm in an air-jet mill, 250 parts of mometasone furoate which has been similarly ground to a mean particle diameter of 1.5µm and 4738 parts of lactose monohydrate having a particle diameter below 212µm.

Examples 4 - 92

[0034] Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

5	Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
10	4	12	50	4938
	5	12	100	4888
	6	12	150	4838
	7	12	200	4788
15	8	6	50	4944
	9	6	100	4894
	10	6	150	4844
	11	6	200	4794
20	12	6	250	4744
	13	18	50	4932
	14	18	100	4882
25	15	18	150	4832
	16	18	200	4782
	17	18	250	4732
	18	24	50	4926
30	19	24	100	4876
	20	24	150	4826
	21	24	200	4776
35	22	24	250	4726
	23	30	50	4920
	24	30	100	4870
	25	30	150	4820
40	26	30	200	4770
	27	30	250	4720
	28	36	50	4914
45	29	36	100	4864
	30	36	150	4814
	31	36	200	4764
50	32	36	250	4714
	33	6	50	9944
	34	6	100	9894
	35	6	150	9844
55	36	6	200	9794
	37	6	250	9744
	38	12	50	9938

(continued)

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
5	39	12	9888
40	12	150	9838
41	12	200	9788
10	42	12	9738
43	18	50	9932
44	18	100	9882
15	45	18	9832
46	18	200	9782
47	18	250	9732
20	48	24	9926
49	24	100	9876
50	24	150	9826
51	24	200	9776
25	52	24	9726
53	30	50	9920
54	30	100	9870
55	30	150	9820
30	56	30	9770
57	30	250	9720
58	36	50	9914
35	59	36	9864
60	36	100	9814
61	36	150	9764
40	62	36	9714
63	6	50	14944
64	6	100	14894
65	6	150	14844
45	66	6	14794
67	6	200	14744
68	6	250	14788
69	12	50	14938
50	70	12	14888
71	12	100	14838
72	12	150	14788
73	18	50	14738
55	74	18	14932
75	18	100	14882
		150	14832

(continued)

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
5 76	18	200	14782
77	18	250	14732
78	24	50	14926
10 79	24	100	14876
80	24	150	14826
81	24	200	14776
15 82	24	250	14726
83	30	50	14920
84	30	100	14870
85	30	150	14820
20 86	30	200	14770
87	30	250	14720
88	36	50	14914
25 89	36	100	14864
90	36	150	14814
91	36	200	14764
92	36	250	14714

Example 93

[0035] Gelatin capsules suitable for use in a capsule inhaler such as that described in US3991761 are prepared, each capsule containing a dry powder obtained by mixing 12 $\mu$ g of formoterol fumarate dihydrate which has been ground to a mean particle diameter of 1 to 5 $\mu$ m in an air jet mill, 250 $\mu$ g of mometasone furoate which has been similarly ground to a mean particle diameter of 1 to 5 $\mu$ m and 24738 $\mu$ g of lactose monohydrate having a particle diameter below 212 $\mu$ m.

Examples 94 - 152

[0036] Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example :

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
45 94	12	50	24938
95	12	100	24888
96	12	150	24838
50 97	12	200	24788
98	6	50	24944
99	6	100	24894
100	6	150	24844
55 101	6	200	24794
102	6	250	24744

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(continued)

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
5	103	18	50
	104	18	100
	105	18	150
10	106	18	200
	107	18	250
	108	24	50
15	109	24	100
	110	24	150
	111	24	200
20	112	24	250
	113	30	50
	114	30	100
	115	30	150
25	116	30	200
	117	30	250
	118	36	50
30	119	36	100
	120	36	150
	121	36	200
	122	36	250
35	123	6	50
	124	6	100
	125	6	150
40	126	6	200
	127	6	250
	128	12	50
	129	12	100
45	130	12	150
	131	12	200
	132	12	250
	133	18	50
50	134	18	100
	135	18	150
	136	18	200
55	137	18	250
	138	24	50
	139	24	100
			19876

(continued)

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
5	140	24	150
	141	24	200
	142	24	250
10	143	30	50
	144	30	100
	145	30	150
15	146	30	200
	147	30	250
	148	36	50
20	149	36	100
	150	36	150
	151	36	200
25	152	36	250
			19714

Examples 153 - 176

[0037] Example 3 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
30	153	6	25
	154	6	50
	155	6	100
35	156	6	150
	157	6	200
	158	6	250
40	159	12	25
	160	12	50
	161	12	100
45	162	12	150
	163	12	200
	164	12	250
50	165	12	300
	166	12	350
	167	12	400
55	168	24	25
	169	24	50
	170	24	100
			2876

(continued)

Example	Formoterol Fumarate Dihydrate (Parts)	Mometasone Furoate (Parts)	Lactose Monohydrate (Parts)
5	171	24	150
	172	24	200
	173	24	250
	174	24	300
	175	24	350
	176	24	400

## 15 Examples 177-281

[0038] Example 93 is repeated, but using the amounts of the ingredients shown in the table below in place of the amounts used in that Example:

Example	Formoterol Fumarate Dihydrate (µg)	Mometasone Furoate (µg)	Lactose Monohydrate (µg)
20	177	6	25
	178	6	50
	179	6	100
	180	6	150
	181	6	200
	182	6	250
25	183	6	300
	184	6	350
	185	6	400
	186	12	25
	187	12	50
	188	12	100
30	189	12	150
	190	12	200
	191	12	250
	192	12	300
	193	12	350
	194	12	400
35	195	12	500
	196	24	25
	197	24	50
	198	24	100
	199	24	150
	200	24	200
40	201	24	250
	202	24	300
	203	24	350
	204	24	400
	205	24	450
	206	24	500
45	207	24	550
	208	24	600
	209	24	650
	210	24	700
	211	24	750
	212	24	800
50	213	24	850
	214	24	900
	215	24	950
	216	24	1000
	217	24	1050
	218	24	1100
55	219	24	1150
	220	24	1200
	221	24	1250
	222	24	1300
	223	24	1350
	224	24	1400

(continued)

Example	Formoterol Fumarate Dihydrate (µg)	Mometasone Furoate (µg)	Lactose Monohydrate (µg)
5	203	6	25
	204	6	50
	205	6	100
	206	6	150
10	207	6	200
	208	6	250
	209	6	300
15	210	12	25
	211	12	50
	212	12	100
	213	12	150
20	214	12	200
	215	12	250
	216	12	300
25	217	12	400
	218	12	500
	219	24	25
30	220	24	50
	221	24	100
	222	24	150
	223	24	200
35	224	24	250
	225	24	300
	226	24	400
40	227	24	500
	228	6	25
	229	6	50
	230	6	100
45	231	6	150
	232	6	200
	233	6	250
50	234	6	300
	235	6	400
	236	6	500
55	237	12	25
	238	12	50
	239	12	100
	240	12	200
			4788

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(continued)

Example	Formoterol Fumarate Dihydrate (µg)	Mometasone Furoate (µg)	Lactose Monohydrate (µg)
241	12	300	4688
242	12	400	4588
243	12	500	4488
244	12	25	24963
245	12	300	24688
246	12	400	24588
247	12	500	24488
248	12	25	19963
249	12	300	19688
250	12	400	19588
251	12	500	19488
252	6	600	4394
253	6	800	4194
254	12	600	4388
255	12	800	4188
256	24	600	4376
257	24	800	4176
258	6	600	9394
259	6	800	9194
260	12	600	9388
261	12	800	9188
262	24	600	9376
263	24	800	9176
264	6	600	14394
265	6	800	14194
266	12	600	14388
267	12	800	14188
268	24	600	14376
269	24	800	14176
270	6	600	19394
271	6	800	19194
272	12	600	19388
273	12	800	19188
274	24	600	19376
275	24	800	19176
276	6	600	24394
277	6	800	24194
278	12	600	24388

(continued)

Example	Formoterol Fumarate Dihydrate (µg)	Mometasone Furoate (µg)	Lactose Monohydrate (µg)
279	12	800	24188
280	24	600	24376
281	24	800	24176

10 **Claims**

1. A medicament containing, separately or together, (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or a solvate of said salt and (B) mometasone furoate, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.
2. A medicament according to claim 1 which is a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B), optionally together with a pharmaceutically acceptable carrier.
3. A medicament according to claim 1 or 2, in which (A) is formoterol fumarate dihydrate.
4. A medicament according to claim 1, 2 or 3, which is in inhalable form and is
  - (i) an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant; or
  - (ii) a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium or a combination of a dispersion of (A) in said medium with a dispersion of (B) in said medium; or
  - (iii) a dry powder comprising finely divided (A) and/or (B) optionally together with a pharmaceutically acceptable carrier in finely divided form.
5. A medicament according to claim 4, in which the inhalable form is the aerosol (i) and the propellant is a halogen-substituted hydrocarbon in which (A) and/or (B) is dispersed.
6. A medicament according to claim 4, in which the inhalable form is the dry powder (iii), in which the carrier is present and is a saccharide.
7. A medicament according to claim 4 in which the inhalable form is an aerosol (i) or a dry powder (iii) and (A) and/or (B) has an average particle diameter up to 10 µm.
8. A medicament according to any one of the preceding claims, in which the weight ratio of (A) to (B) is from 2:1 to 1:2000.
9. A medicament according to claim 2, which is a dry powder in a capsule, the capsule containing from 3 to 36 µg of (A) as formoterol fumarate dihydrate, from 25 µg to 800 µg of (B) and a pharmaceutically acceptable carrier in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50 mg.
10. A medicament according to claim 2, which is a dry powder comprising, by weight, from 3 to 36 parts of (A) as formoterol fumarate dihydrate, from 25 to 800 parts of (B) and 2164 to 24972 parts of a pharmaceutically acceptable carrier.
11. A pharmaceutical kit comprising (A) as defined in claim 1 or 3 and (B) as defined in claim 1 in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts, together with one or more inhalation devices for administration of (A) and (B).
12. The use of (A) as defined in claim 1 or 3 and (B) as defined in claim 1 for the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration in the treatment of an inflammatory

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**or obstructive airways disease.**

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## EUROPEAN SEARCH REPORT

Application Number  
EP 03 00 3950

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